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SULPHOCONJUGATION AS A TEST OF LIVER FUNCTION.

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OF the various functions of the liver, its detoxicating influence is one of the most important, and one also, to which very much attention has been devoted. It is quite well known that toxic radicals liberated during the process of normal or abnormal intestinal digestion are carried to the liver by means of the portal circulation, and there either neutralized or oxidized or conjugated, etc., to lessen or remove the toxic influence of the substance. One of these methods of detoxication is the union of aromatic radicals with sulphuric acid and their excretion in the form of conjugated sulphates (ethereal sulphates) in the urine.

Since Städeler found phenol in cows' and horses' urine, Landolt, Lieben, Hoppe-Seyler, Buliginsky, and Munk found traces of it in normal human urine, and Salkowski observed that in ileus and other obstructive intestinal disease the excretion of phenol in the urine is much increased.

This formation of phenol and phenolic substances, cresol, indol, skatol, etc., has been ascribed to the action of intestinal bacterial flora. Such organism like the *B. coli communis*, which is a normal inhabitant of the intestinal canal, are harmless under ordinary circumstances. In conditions of injury to the intestinal mucosa these organisms become virulent (Fermi and Salto). Other organisms, like the *B. putrificus*, the *B. aërogenes capsulatus*, which are obligatory anaërobes, thrive in the colon when there is no oxygen (Herter) and break up protein into the carbocyclic, toxic substances.

It was demonstrated by Baumann that these split products are very toxic, but that when they are united with sulphuric acid they have lost their poisonous effect. Baumann found that phenol sulphate is a normal urinary constituent and that the administration of phenol increases the elimination of phenol sulphate in the urine. Baumann and Herter reported that not only phenol, but also other substances were excreted in the urine as conjugated sulphates. They also observed that phenol unites not only with sulphuric acid but also with other radicals. This was confirmed by Schmiedeberg, who found that phenol unites with glycuronic acid. Upon poisoning dogs with phenol, Baumann found that the liver became rich in phenol sulphates. For example, in 100 parts of liver he found nineteen times as much tribromphenol as in 100 parts of blood. This observation seemed to prove that the liver is the seat of conjugation of phenolic and indolic radicals with sulphuric acid. The results of other scientists were, however, contradictory, as will be seen from the following references:

Lang determined the quantity of ethereal sulphates in the urine of geese before and after extirpation of the liver. Though his analytical differences are rather small, and should not be taken conclusively, still he was led to believe that the synthesis of the ethereal sulphates was not exclusively performed in the liver.

In experiments performed *in vitro* Kochs also demonstrated, so it appeared to him, that the liver was not the only seat of sulphoconjugation. He took portions of liver, kidney, pancreas, thymus, muscles, and minced each organ respectively and added phenol and disodium sulphate. He kept these mixtures at body temperature or else at 8° to 12° C. He reported that all the tissues save the thymus took part in the synthesis. He obtained the same results with ortho-, meta-, and para-dioxyphenol.

Landi repeated the experiments of Kochs, using, however, only liver tissue. But, as he says, due to the fact that the decomposition sets in so very soon, he could not confirm Kochs' findings. In order to throw more light on the subject he made perfusion experiments with the liver, and he came to the final conclusion that the seat of conjugation of the phenolic and sulphuric acid radicals was not the liver but the intestines.

The observations of Landi found no confirmation and were directly contradicted by the results of Embden and Glaessner. They performed perfusion experiments on the organs of dogs, using the liver, kidneys, muscle, lungs, and small intestines. From their investigations they concluded that the liver was the most important organ for the formation of the ethereal sulphates. Smaller quantities of ethereal sulphates are produced in the lungs and the kidneys, but the muscle tissue and the small intestine play a very insignificant role in the production of the ethereal sulphates. Reale, from his observations, was firmly convinced that the liver was the seat of the synthesis of the conjugated ethereal sulphates.

In normal conditions of the alimentary tract, Strauss and Philipsohn found no phenol in the urine of human beings, and they concluded that under normal conditions the phenol and other radicals were conjugated with sulphuric acid. According to these authors the liver is the seat of this conjugation.

Herter and Wakeman took 7 grams of liver, kidney, muscle, brain, and blood respectively, which they minced, and treated each tissue with 10 c.c. of a weak phenol solution, and allowed to stand for two to three hours. The mixtures were then distilled, and they found that there was a loss in the phenol distilled over. The liver retained most of the phenol, then came in order the kidneys, muscle, and brain.

In hepatic disease there have been observed disturbances in the elimination of the ethereal sulphates. In conditions of jaundice Biernacki found four times as much ethereal sulphates as normally. Darenberg and Perroy found an increased excretion of indol and skatol in the urine of jaundiced individuals. Labbe and Vitry obtained similar results. Magrageas obtained varying amounts of ethereal sulphates in icteric patients.

The question has been discussed by Eiger and Hopazde whether the aromatic compounds formed in the system are diminished in amount and destroyed under normal conditions of hepatic activity, and whether in cases of disturbances of the function of the liver, these compounds are obviously increased and placed at the disposal of the liver for conjugation with sulphuric acid. The subject is important in its relation to cases of disease of the hepatic parenchyma, more so than in cases of simple biliary stasis. The ethereal sulphuric acids are most frequently, both absolutely and relatively, increased in atrophic cirrhosis of the liver, and most markedly in tumors of the liver.

Finizio studied the excretion of ethereal sulphates in normal individuals, in a patient suffering with an echinococcus cyst of the liver, and in cases of hepatic cirrhosis. He found that when he administered thymol to the normal or echinococcic individual there was a marked increase in the ethereal sulphate output in the urine, whereas the cirrhosis patient showed no such increase.

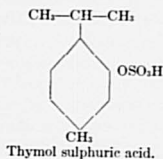
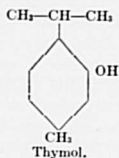
It has been quite definitely established that normally the inorganic sulphates of the urine form about 70 per cent. of the total sulphur and the remaining 30 per cent. are divided almost equally between the ethereal sulphates and the neutral sulphur.

It is, of course, impossible to rely upon the excretion of ethereal sulphates as an index of hepatic function. The proteins that are ingested daily give rise to their quota of aromatic radicals which influence the quantity of the conjugated sulphates excreted.

It has seemed to me advisable, therefore, to administer a definite quantity of an aryl compound and to examine the urine for the conjugated products of this substance. For the purposes of

this work thymol seems to be the most suitable aromatic substance to use.

Thymol is meta-isopropyl-cresol. Baumann and Herter have found that thymol sulphuric acid occurs in the urine of rabbits after thymol administration. Vogelius reported that the feeding of 0.5 gram thymol increases the output of ethereal sulphates from 0.05 gram to 0.107 gram per 100 c.c. of urine. Blum, Preusse and Finizio have separately reported that thymol is eliminated in the urine as thymol sulphuric acid and as thymol hydroquinone sulphuric acid.



I adopted the following technic for the determination of hepatic sufficiency by means of the ethereal sulphate output.

The patient received a dose of castor oil to clean out his bowels. He was then kept on a known diet for two days, during which time the urine was collected, preserved with a few drops of formaldehyde, and analyzed for total sulphur and ethereal sulphates.¹ On the third day the patient received a capsule containing 0.5 gram thymol. A dose of olive oil is administered to the patient several hours after the thymol dose in order to dissolve the thymol and increase its absorption from the intestinal canal. The urine was collected for the next forty-eight hours, preserved with a little formaldehyde and analyzed for total sulphur and the ethereal sulphates.

If all the thymol were absorbed and if all the thymol were conjugated with sulphuric acid and none with glycuronic acid the 0.5 gram thymol would be excreted as 0.7666 gram thymol sulphuric acid. This would cause a marked increase in the percentage of the ethereal sulphates. If the liver were not functioning properly the thymol would not be conjugated and the percentage of ethereal sulphates would be only slightly different from what it had been on the first two days.

It is probable that each individual cell of the hepatic parenchyma takes part in all of the liver functions; it is possible, however, that different portions of the liver lobule may have specific functions. In the former case it is most likely that a reduction in the ability of the liver to perform one function will be accompanied by a proportional reduction in all the liver functions; in the latter case one or

¹ The total sulphur was analyzed by Benedict's method, and the ethereal sulphates by Folin's method.

more functions of the liver may be disturbed without affecting the other hepatic functions. One objection to the study of the function of any organ as an index of disease of that organ is that it is perhaps possible for the healthy portion of the diseased organ to compensate and assume the work of the whole gland. In such a condition, of course, the functional capacity of the organ may be normal and would be no index of the pathological changes in that organ. Under these circumstances only marked destructive changes would leave their impress on the functional sufficiency of the organ.

ETHEREAL SULPHATE ELIMINATION BEFORE AND AFTER THYMOL ADMINISTRATION.

Case No.	Diagnosis.	Total sulphur, gms.		Ethereal sulphate sulphur, gms.		Ethereal sulphate sulphur, per cent.	
		Before thymol.	After thymol.	Before thymol.	After thymol.	Before thymol.	After thymol.
1	Normal	2.0375	2.1295	0.2893	0.5646	14.2	26.8
2	Gastritis	1.9428	1.7427	0.1457	0.3380	7.5	19.4
3	Fracture	2.7467	2.5527	0.3131	0.6024	11.4	23.6
4	Congestion of liver	0.9852	0.0734	0.1753	0.7069	17.8	26.8
5	Congestion of liver	1.7345	1.6982	0.2480	0.3610	14.3	21.2
6	Gall-stones	2.7628	2.8075	0.7597	1.0303	27.5	36.7
7	Gall-stones	3.0042	2.6826	0.3965	0.8474	13.2	29.4
8	Cholecystitis	2.7807	2.6437	0.4866	0.7428	17.5	28.1
9	Atrophic cirrhosis	2.2328	2.3029	0.2791	0.3400	12.5	15.2
10	Tumor of liver	1.9492	1.8757	0.1637	0.3676	8.4	19.6
11	Cancer of liver	2.7526	2.6278	0.6083	0.6648	22.1	25.3
12	Syphilis of liver	2.8104	2.9075	0.3990	0.5437	14.2	18.7

The results that we have obtained in the cases cited in the accompanying table are very encouraging. The work is now in progress. We are collecting comparative data as to the positive incidence of this test and other tests of liver sufficiency in the same case of hepatic disease.

SOME CLINICAL AND EXPERIMENTAL OBSERVATIONS ON GASTRIC ACIDITY USE OF THE GAS-CHAIN METHOD.

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IN order to determine the effect produced by chronic inflammatory and altered physiological changes in the gastro-intestinal tract, I have undertaken the study of the gastric secretion in such conditions by means of the exact gas-chain method of determining the acidity and have plotted curves, comparing the results with those gained by